ANTI-VEGF AND BEYOND:

EXPANDING THERAPEUTIC OPTIONS FOR WET AMD

A 2025 review of clinical trials evaluating novel therapies for wet AMD.

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After 20 years of therapy with anti-VEGF agents, the landscape for wet AMD management is now transforming from anti-VEGF monotherapy to a diverse pipeline of novel disease targets and innovative delivery technologies. In this article, we summarize the spectrum of emerging therapies for wet AMD (Table), including biosimilars, gene therapy, tyrosine kinase inhibitors (TKIs), and other novel drug targets.

GENE THERAPIES

Current investigational gene therapies for wet AMD employ a one-time administration (intravitreal, subretinal, or suprachoroidal) of an adeno-associated viral (AAV) vector carrying non-integrating transgenes encoding anti-VEGF proteins or multitarget constructs. By enabling continuous intraocular production of these therapeutics, gene therapy may greatly reduce or eliminate anti-VEGF injection burden in patients with wet AMD.

4D-150 (4D Molecular Therapeutics) is an intravitreally delivered AAV R100 vector containing an aflibercept/anti-VEGF-C miRNA transgene. In the phase 1/2 PRISM trial (NCT05197270) 4D-150 reduced the injection burden by 83% and eliminated injections entirely in 57% of patients, compared with aflibercept (Eylea, Regeneron) every 8 weeks.[1] The phase 3 4FRONT-1 (NCT06864988) and 4FRONT-2 (NCT07064759) trials are enrolling.[2]

ABBV-RGX-314 (sura-vec, Regenxbio/Abbvie) contains a

AT A GLANCE

- By enabling continuous intraocular production of anti-VEGF proteins, gene therapy may greatly reduce or eliminate anti-VEGF intravitreal injection burden in patients with wet AMD.
- Tyrosine kinase inhibitors, which block receptor-mediated (ie, VEGFR) signaling by decreasing receptor phosphorylation, may have the potential to augment and replace existing therapies.
- Novel drug delivery methods include suprachoroidal, subretinal, topical, and even subcutaneous routes.

THE RETINA PIPELINE

TABLE. SUMMARY OF WET AMD THERAPIES IN DEVELOPMENT (AS OF NOVEMBER 2025)

Therapy (Company)	Drug Type/Mechanism	Delivery Method	Trial Identifier	Trial Status	Primary Completion
Phase 3					
4D-150 (4D Molecular Therapeutics)	Gene therapy	Intravitreal	NCT06864988 NCT07064759	Recruiting	June 2027 November 2028
ABBV-RGX-314 (Regenxbio/Abbvie)	Gene therapy	Subretinal	NCT05407636 NCT04704921	Recruiting	October 2026 December 2026
ADVM-022 (Adverum)	Gene therapy	Intravitreal	NCT06856577	Recruiting	December 2026
EYP-1901 (EyePoint)	Tyrosine kinase inhibitor	Implant	NCT06668064 NCT06683742	Active, not recruiting	August 2026 October 2026
IBI302 (Innovent Biologics)	Fusion protein	Intravitreal	NCT05972473	Active, not recruiting	February 2027
KSI-301/KSI-501 (Kodiak Sciences)	Anti-VEGF-A/fusion protein	Intravitreal	NCT06556368	Active, not recruiting	August 2026
OTX-TKI (Ocular Therapeutix)	Tyrosine kinase inhibitor	Implant	NCT06223958 NCT06495918	Active, not recruiting	April 2026 January 2027
RC28-E (RemeGen)	Anti-VEGF/fibroblast growth factor 2	Intravitreal	NCT05727397	Recruiting	November 2025
Phase 2					
CLS-AX (Clearside Biomedical)	Tyrosine kinase inhibitor	Suprachoroidal	NCT05891548	Complete	
D-4517.2 (Ashvattha Therapeutics)	Tyrosine kinase inhibitor	Subcutaneous	NCT05387837	Active, not recruiting	May 2025
ISTH0036 (Isarna)	Antisense oligonucleotide	Intravitreal	EudraCT 2021-001213-36	Complete	
RBM-007 (Ribomic)	Anti-fibroblast growth factor 2	Intravitreal	NCT04200248	Complete	
SYL1801 (Sylentis)	siRNA	Topical	NCT05637255	Complete	
TO-0-1002 (Theratocular Biotek)	Tyrosine kinase inhibitor	Topical	NCT05390840	Unknown status	March 2024
Phase 1 and 1/2					
AM712 (AffaMed)	Anti-VEGF/angiopoietin-2	Intravitreal	NCT05345769	Complete	
AR-14034 (Alcon)	Tyrosine kinase inhibitor	Implant	NCT05769153	Recruiting	September 2027
AXT107 (AsclepiX Therapeutics)	VEGF-A/C inhibiting and Tie2 activating	Suprachoroidal	NCT05859776	Active, not recruiting	March 2025
CG-P5 (Caregen)	VEGFR2-inhibitor	Topical	NCT06132035	Recruiting	May 2025
Episcleral brachytherapy	Focal radiation	Episcleral	NCT02988895	Unknown status	May 2023
EXG102-031 (Exegenesis Bio)	Gene therapy	Subretinal	NCT05903794	Active, not recruiting	February 2026
FT-003 (Frontera Therapeutics)	Gene therapy	Intravitreal	NCT06492863	Recruiting	October 2024
HG202 (HuidaGene Therapeutics)	Gene therapy	Subretinal	NCT06031727 NCT06623279	Recruiting Not yet recruiting	June 2025 February 2027
KH631 (Chengdu Origen/Vanotech)	Gene therapy	Subretinal	NCT05657301	Recruiting	September 2026
KH658 (Chengdu Origen/Vanotech)	Gene therapy	Suprachoroidal	NCT06458595 NCT06825858	Recruiting Not yet recruiting	March 2026 Unknown
Lenvatinib (AiViva BioPharma)	Tyrosine kinase inhibitor	Periocular gel	NCT05698329	Active, not recruiting	March 2025
MK-3000 (EyeBio/Merck)	Anti-FZD4, LRP5, and TSPAN12 Wnt agonist	Intravitreal	NCT05919693	Complete	
OLX10212 (OliX Pharmaceuticals)	siRNA	Intravitreal	NCT05643118	Recruiting	November 2024
PAN 90806 (PanOptica/Zhaoke)	Tyrosine kinase inhibitor	Topical	NCT03479372	Complete	
Recently Discontinued Programs					
AR-13503 (Aerie/Alcon)	Rho kinase and protein kinase C inhibitor	Implant	NCT03835884	Complete	
AKST4290 (Alkahest)	CCR3 inhibitor	Oral	NCT04331730	Complete	
OPT-302 (Opthea)	Anti-VEGF-C/D	Intravitreal	NCT04757610 NCT04757636	Terminated	
UBX1325 (Unity Biotechnology)	B-cell lymphoma-extra-large inhibitor	Intravitreal	NCT05275205	Complete	

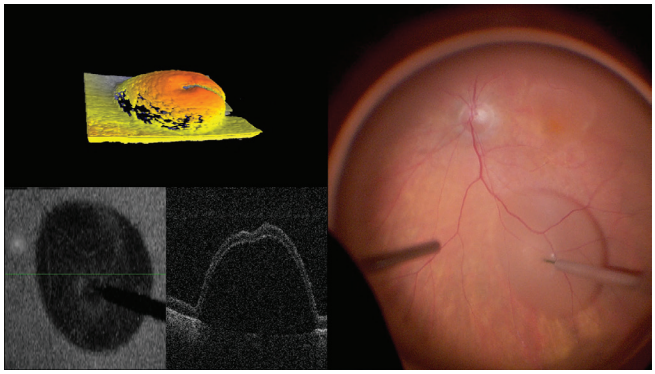

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Figure. Intraoperative OCT can help clinicians ensure proper subretinal bleb formation during treatment with gene therapy.

ranibizumab-like protein transgene delivered subretinally or suprachoroidally via an AAV8 vector (Figure). The phase 2b/3 ATMOSPHERE (NCT04704921) and phase 3 ASCENT (NCT05407636) trials are assessing noninferiority of subretinal ABBV-RGX-314 to monthly ranibizumab (Lucentis, Genentech/Roche) and bimonthly aflibercept, respectively. In the phase 2 AAVIATE trial (NCT04514653), suprachoroidal delivery of ABBV-RGX-314 led to a reduction or elimination of supplemental anti-VEGF injections in 80% and 50% of patients, respectively, over 6 months compared with monthly ranibizumab.[3]

ADVM-022 (ixo-vec, Adverum) contains an aflibercept transgene delivered intravitreally using the AAV2.7m8 vector. In the phase 2 LUNA trial (NCT05536973), ADVM-022 led to an 80% reduction in supplemental anti-VEGF injections over 52 weeks compared with patients' prior injection burden. Additionally, 50% of patients remained injection free.[4] The phase 3 ARTEMIS trial (NCT06856577) is enrolling.

FT-003 (Frontera Therapeutics) is an intravitreally delivered AAV2.7m8 vector containing an aflibercept transgene. Interim data from a phase 1/2 trial (NCT06492863) demonstrated an 80% reduction in the need for supplemental aflibercept injections, along with improvements in BCVA and retinal structure.[5]

Several gene therapies are in phase 1 trials, including EXG102-031 (Exegenesis Bio; NCT05903794), HG202 (HuidaGene Therapeutics; NCT06031727 and NCT06623279), KH631 (Chengdu Origen/Vanotech; NCT05657301), and KH658 (Chengdu Origen/Vanotech; NCT06825858 and NCT06458595).

BISPECIFIC AND TRISPECIFIC DRUGS

Anti-VEGF therapy coupled with alternative pathway targeting is a promising strategy to improve efficacy of wet AMD therapies; this approach was recently validated with the approval of faricimab (Vabysmo, Genentech/Roche), a bispecific VEGF-A/angiopoietin-2 antibody. Others are under investigation, including the following:

KSI-301 (tarcocimab tedromer, Kodiak Sciences) is an intravitreally delivered anti-VEGF-A antibody, which did not meet its primary endpoint of noninferiority to 8-week dosing of aflibercept based on BCVA in the phase 2b/3 DAZZLE trial (NCT04049266).[6] The phase 3 DAYBREAK trial (NCT06556368) is assessing adjusted dosing and trial design with a primary endpoint of noninferiority to aflibercept based on BCVA.

KSI-501 (tabirafusp tedromer, Kodiak Sciences) is also under investigation as part of the DAYBREAK trial. This therapy is an intravitreal bispecific VEGF trap/anti-interleukin-6 fusion protein.

IBI302 (efdamrofusp alfa, Innovent Biologics) is an intravitreal recombinant fusion protein containing decoy VEGFR and a complement receptor 1 domain to reduce VEGF and C3b/C4b activation. In a phase 2 trial (NCT05403749), IBI302 showed noninferiority to every-8-week aflibercept based on BCVA.[7] The phase 3 STAR trial (NCT05972473) is ongoing.

RC28-E (RemeGen) is an intravitreally delivered decoy receptor trap fusion protein that binds soluble VEGF and fibroblast growth factor 2. An open-label phase 1 clinical trial showed evidence of improvements in BCVA and retinal anatomic parameters.[8] A phase 3 trial (NCT05727397) is assessing noninferiority of RC28-E with aflibercept based on BCVA.

AXT107 (AsclepiX Therapeutics) is a suprachoroidally injected, integrin-regulating peptide that inhibits VEGF-A/C and activates Tie2 signaling and has completed recruitment in phase 1/2 testing in the DISCOVER trial (NCT05859776).

AM712 (AffaMed) is a recombinant humanized monoclonal antibody targeting VEGF and angiopoietin-2 that showed improvements in BCVA, central subfield thickness (CST), and anti-VEGF dosing frequency in the phase 1 CONQUER trial (NCT05345769).[9]

TYROSINE KINASE INHIBITORS

TKIs block receptor-mediated (ie, VEGFR) signaling by decreasing receptor phosphorylation. These drugs may have the potential to augment or replace existing anti-VEGF or multitarget therapies.

EYP-1901 (Duravyu, EyePoint Pharmaceuticals) is a semiannually administered intravitreal implant containing the TKI vorolanib. In the phase 2 DAVIO2 trial, EYP-1901 demonstrated noninferiority to aflibercept and reduced supplemental anti-VEGF injection burden by approximately 80%.[10] The phase 3 LUCIA (NCT06683742) and LUGANO (NCT06668064) trials are fully enrolled.

OTX-TKI (Axpaxli, Ocular Therapeutix) is an intravitreal hydrogel implant containing axitinib. In a phase 1 trial (NCT04989699), treatment with OTX-TKI showed noninferiority to aflibercept and led to an 89% reduction in anti-VEGF injection burden.[11] The phase 3 SOL-1 (NCT06223958) and SOL-R (NCT06495918) trials are ongoing.

ANTI-VEGF BIOSIMILARS

Two ranibizumab (Lucentis, Genentech/Roche) and six aflibercept (Eylea, Regeneron) biosimilars are FDA approved in the United States and several others have been approved in the European Union (Table). The bevacizumab (Avastin, Genentech/Roche) biosimilar Lytenava (ONS-5010, Outlook Therapeutics) is approved for intravitreal use by the European Medicines Agency, and the company was recently issued a complete response letter by the FDA in August 2025.

TABLE. FDA- AND EMA-APPROVED ANTI-VEGF BIOSIMILARS

Drug Name (Biologic, Company)	FDA Approved	EMA Approved
Aflibercept Biosimilars		
Afqlir/Enzeevu (aflibercept-abzv, Sandoz)	✓	✓
Afiveg (Stada)	X	✓
Ahzantive/Baiama (aflibercept-mrbb, Formycon/Klinge)	✓	✓
Eiyzey/Vgenfli (Polpharma/Sandoz)	X	✓
Eydenzelt (aflibercept-boav, Celltrion)	✓	✓
Eyluxvi (Alteogen)	X	✓
Mynzepli (aflibercept-tvnh, Alvotech)	X	✓
Opuviz (aflibercept-yszy, Samsung Bioepis/Biogen)	✓	✓
Pavblu (aflibercept-ayyh, Amgen)	✓	✓
Yesafili (aflibercept-jbvf, Biocon Biologics)	✓	✓
Ranibizumab Biosimilars		
Byooviz (ranibizumab-nuna, Samsung Bioepis/Biogen)	✓	✓
Cimerli (ranibizumab-eqrn, Sandoz)	✓	X
Epruvy (Midas Pharma)	X	✓
Ranivisio (Bioeq)	X	✓
Rimmyrah (Qilu Pharma)	X	✓
Ximluci (Stada/Xbrane Biopharma)	X (Received CRL)	✓
Bevacizumab Biosimilars		
Lytenava (bevacizumab-vikg, Outlook Therapeutics)	X (Received CRL)	✓

Abbreviations: EMA, European Medicines Agency; CRL, complete response letter.

CLS-AX (axitinib, Clearside Biomedical) is a suprachoroidally delivered TKI. In the phase 2b ODYSSEY trial (NCT05891548), treatment with CLS-AX was noninferior to aflibercept every 8 weeks based on BCVA and led to an 84% reduction in anti-VEGF injections.[12]

D-4517.2 (migaldendranib, Ashvattha Therapeutics) is a subcutaneously administered TKI that bioaccumulates within choroidal neovascularization. In a phase 2 trial (NCT05387837), treatment with D-4517.2 led to a 69% reduction in supplemental aflibercept injections compared with patients' injection history, with stable BCVA and CST.[13]

TO-O-1002 (MG-O-1002, Theratocular Biotek) is a TKI delivered as a topical eye drop three times a day. In a phase 2a study (NCT05390840), TO-O-1002 was shown to reduce the need for supplemental anti-VEGF injections by 86% compared with a placebo drop.[14]

KHK4951 (tivozanib, Kyowa Kirin Group) is another topical TKI in a phase 2 trial (NCT06116890) evaluating high, middle, and low doses. The primary outcome is the reduction of 15 or more letters in BCVA at week 44; secondary

outcomes include the need for intravitreal aflibercept and OCT and fluorescein angiography changes.

Other TKIs in early-phase investigations include AR-14034 (axitinib, Alcon; NCT05769153), PAN-90806 (PanOptica/Zhaoke; NCT03479372), and lenvatinib (AIV-007, AiViva BioPharma; NCT05698329).

NOVEL DRUG TARGETS AND DELIVERY MODALITIES

Innovation continues for novel drug targets, offering the opportunity to expand the therapeutic repertoire outside of mainstay anti-VEGF therapy.

ISTH0036 (Isarna) is an intravitreally administered antisense oligonucleotide that reduces expression of TGF-β2 to reduce profibrotic signaling. In a recent phase 2a trial (EudraCT 2021-001213-36), ISTH0036 led to a 70% decrease in subretinal hyperreflective material, stable or improved BCVA, and decreased CST relative to baseline.[15]

RBM-007 (umedaptanib pegol, Ribomic) is an intravitreally delivered pegylated anti-FGF-2 RNA aptamer with antifibrotic activity. In the phase 2 TOFU (NCT04200248) and RAMEN (NCT04640272) trials, RBM-007 did not show a benefit over aflibercept alone. The TEMPURA open-label extension study (NCT04895293) showed BCVA and CST stabilization or improvements compared with baseline in anti-VEGF-naïve patients.[16]

SYL1801 (Sylentis) is a daily eye drop containing an anti-NRARP siRNA that modulates notch-Wnt crosstalk to reduce angiogenesis; the phase 2a trial (NCT05637255) showed stabilization or improvements in BCVA compared with baseline.[17]

MK-3000 (Restoret, EyeBio/Merck) is an intravitreal anti-FZD4/ LRP5/TSPAN12 antibody that activates canonical Wnt signaling. In the phase 1/2 AMARONE trial (NCT05919693), MK-3000 in combination with monthly aflibercept resulted in improved BCVA and decreased CST.[18]

OLX10212 (OliX Pharmaceuticals) is an intravitreally delivered siRNA targeting an undisclosed target involved in inflammation, which is currently undergoing phase 1 testing (NCT05643118).

CG-P5 (Caregen) is a once-daily eye drop containing a VEGFR2-inhibiting peptide. A phase 1 study (NCT06132035) is assessing the safety of CG-P5 compared with a placebo drop or monthly aflibercept.

Episcleral brachytherapy (Salutaris Medical Devices) involves the delivery of transscleral radiation to reduce actively proliferating, pathological cells within areas of choroidal neovascularization. In the phase 1 NEAMES trial (NCT02988895), this focal radiation treatment reduced anti-VEGF injection burden compared with patient history.[19]

LOOKING AHEAD

The wet AMD treatment landscape is rapidly shifting toward highly durable, targeted, and potentially curative approaches. As we enter 2026, key phase 3 readouts and potential regulatory approvals could mark the beginning of a new era, one in which anti-VEGF monotherapy is augmented by an armamentarium of complementary therapies that can be tailored to the needs of an individual patient. ■

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